

REMARKS

The Office Action of March 11, 2005 presents the examination of claims 6,43 and 46-77.

Claims 43 and 46 are indicated as allowable. The present paper amends claims 52, 53, 61 and 73 and adds claims 78-86.

Support for amendments and the new claims

Claim 52 is amended to recite “An isolated” nucleic acid, correcting an editorial omission.

Claims 53 and 61 are amended to insert the term “hybridizes”, correcting an apparent editorial error.

Claim 73 is amended to recite that the method of metabolic modification is effected by inserting the recited nucleic acid “into a host organism or a cell thereof, so that the content of raffinose family oligosaccharides in the host organism or cell thereof is changed.” Such language is found also in the previously pending claim 74 and for example, at page 7, lines 7-8, of the specification.

New claims 78-86 recite a subset of the nucleic acids that are listed in the previously pending claims 52, 53, 59, 61, 65, 66, 73, 74 and 77, respectively. Therefore, no new matter is added by these new claims.

Rejection under 35 U.S.C. § 101

Claims 46-51 are rejected under 35 U.S.C. § 101, for alleged lack of utility. This rejection is respectfully traversed. Reconsideration and withdrawal thereof are requested.

In particular, the Examiner takes a position that, because there exists a superfamily of proteins in plants that encompasses stachyose synthases (STSs) in addition to the raffinose synthases (RFSs) of the invention, the asserted utility of the presently claimed nucleic acids is not established. The Examiner asserts that the degree of sequence identity among the STSs and among the RFSs is sufficiently low that one kind of enzyme is not distinguishable from the other kind of enzyme merely on the basis of the amino acid sequence encoded by the nucleic acid that is the subject matter of the present claims. The Examiner asserts that the Applicant has not specified a structure-function relationship sufficient to identify the genus of the nucleic acids of the invention.

Applicants strongly disagree with the Examiner.

The present claims 46-51 recite defined amino acid sequences or specific nucleotide sequences that are one sequence that may encode the defined amino acid sequence. The nucleic acid sequences are those of the raffinose synthase cDNAs cloned from soybean, Japanese Artichoke and corn, as in Examples 7, 9 and 11 of the specification; the amino acid sequences are those obtained by translation of the cDNA sequences.

As to the “structure-function relationship” defining the genus of the nucleic acids encoding a raffinose synthase, Applicants do not see how this applies to the present claims 46-51. As explained above, a distinct structure of a particular amino acid sequence or of a particular nucleic acid sequence is recited in these claims.

There is substantial evidence of record that one of ordinary skill in the art can distinguish a RFS enzyme from a STS enzyme solely on the basis of amino acid sequence. Applicants have previously provided phylogenetic analyses of the amino acid sequence of RFSs and STSs and have established that the degree of sequence homology among RFSs and among STSs is significantly higher than the degree of homology between RFSs and STSs. This relationship is robust to analysis using two different sequence identity determination algorithms. See, Table 3 attached to the prior Amendment and Table 2 attached to the Amendment before that one. To this evidence, Applicants now add the Declaration of Mr. Akitsu Nagasawa. Mr. Nagasawa attests to the methodology used to generate the data in Tables 2 and 3 and presents an additional analysis using yet a third approach to calculating sequence identity.

Mr. Nagasawa’s Declaration shows that distinction among RFSs, STSs and SIPs solely upon amino acid sequence data is possible using any of three commonly used sequence homology determination algorithms; CLUSTAL, BLAST (as tBLASTn or BLASTp) and BLAST 2 SEQUENCES. Thus, the ability to distinguish RFSs from STSs (and SIPs) based upon sequence data is robust to the particular analysis program used. Furthermore, the phylogenetic tree generated from the sequence homology analyses shows a deep division

between RFSs and STSs, demonstrating that these two kinds of enzymes are readily distinguishable families based only upon amino acid sequence data.

Accordingly, and as testified by Mr. Nagasawa, the identity of a protein as a raffinose synthase is readily established by analysis of its sequence in comparison to the sequences shown in the present sequences listing, especially by comparison to SEQ ID NO: 2, the identity of which as a raffinose synthase the Examiner does not challenge. The Examiner should also note that the conclusion reached by Mr. Nagasawa is consistent with the text of the specification at page 23, lines 14-17.

The Examiner should not substitute his own judgment for the testimony of one of ordinary skill in the art.

Furthermore, given the amino acid sequence, and identification of any particular protein as a raffinose synthase by virtue of homology to SEQ ID NO:2 (and 4, 6 and 8), the present specification provides an assay for raffinose synthase activity. It can hardly be said that testing of a protein for activity using a disclosed assay method is undue experimentation and one of ordinary skill in the art can readily determine if in fact any one protein having a defined amino acid sequence has the activity of combining a D-galactosyl group through an $\alpha(1 \rightarrow 6)$ bond with a hydroxyl group attached to the carbon atom at position 6 of a D-glucose residue in a sucrose molecule that defines a raffinose synthase enzyme.

Applicants submit that the utility of the invention as described by claims 46-51 is well-established and accordingly the instant rejection should be withdrawn.

Rejection under 35 U.S.C. § 112, first paragraph

Claims 48-77 stand rejected under 35 U.S.C. § 112, first paragraph, for alleged failure of the specification to provide adequate written description support. This rejection is respectfully traversed. Reconsideration and withdrawal thereof are requested.

Applicants have previously argued this rejection in considerable detail in prior responses. Those arguments are reproduced here for convenient review by the Examiner.

From the Amendment filed Feb. 28, 2003:

The Examiner states, "It remains unclear that Applicants have adequately described the genus of plant raffinose synthase genes...." The claims are amended so that the genus of nucleic acids claimed have the specific nucleotide sequences (a) to (h) which encode amino acid sequences of raffinose synthase genes, or a nucleotide sequence hybridizable to a nucleotide sequence complementary to the nucleotide sequence of any one of (a) to (h) under conditions of 0.9 M NaCl, 0.09 M citric acid at 65°C.

Applicants respectfully submit that the amended claims are equivalent to Example 9 of the USPTO "Revised Interim Written Description Guidelines Training Materials." Example 9 of the Training Materials addresses claims that recite the invention in terms of hybridization to a reference sequence. Thus, Example 9 is relevant to the instant claims 1, 30, 32, 36, 40, and 41.

The claim in Example 9 states:

An isolated nucleic acid that specifically hybridizes under highly stringent conditions to the complement of the sequence set forth in SEQ ID NO: 1, wherein said nucleic acid encodes a protein that binds to a dopamine receptor and stimulates adenylate cyclase activity.

This claim language is identical in its general content to that of the instant amended claims. The hybridization conditions set forth in the instant claims are highly stringent. Reference sequences are set forth in the instant claims, as well as a biological activity of a protein.

The disclosure in the instant specification is even more extensive than that described in Example 9. Specifically, in Example 9, the specification discloses only one cDNA that encodes a protein that has the biological activity recited in the claims. On the other hand, in the present application the Inventors have described four variant cDNAs, obtained from four different plant species, that encode proteins having the desired activity. The inventors have further provided examples of PCR primers and detailed description of how to use them to isolate additional examples of isolated DNA encoding raffinose synthase from other species. Working examples (7 and 9-11) of use of the PCR primers to perform such isolations are provided.

For all of the above reasons, Applicants respectfully submit that the instant claims, as amended, fully comply with the requirements of 35 U.S.C. § 112, first paragraph. Thus, the rejection for alleged lack of adequate written description of the claimed invention should be withdrawn.

From the Amendment filed Nov. 12, 2004:

The Examiner takes a position that the specification provides no description of any generic structural feature that confers raffinose synthase activity upon a protein. The Examiner continues to rely upon the *University of California v. Eli Lilly* case. Applicants have already made arguments distinguishing the facts of the present case from those of *Eli Lilly*. The Examiner asserts that the specification fails to describe any complete coding sequence of a raffinose synthase protein other than SEQ ID NO: 1 (or the complete amino acid

sequence of SEQ ID NO: 2). This assertion by the Examiner is simply not correct. SEQ ID NO: 3 present a sequence of a complete raffinose synthase protein. The Examiner seems to know this, as he points only to SEQ ID Nos: 5 and 7 as not being complete sequences. Thus, the primary premise underlying the Examiner's position is not consistent with the actual facts.

Second, the Examiner asserts that the specification is not sufficient to meet Applicants' burden of establishing that the other nucleic acid and amino acid sequences described are actually raffinose synthase genes and proteins, respectively. This argument has been rebutted by the data and explanation thereof provided above.

The rejection has insufficient legal basis for the above reasons and this alone urges that it should not be applied to the present claims.

Moreover, many of the present claims in fact recite structural features that are plainly set forth in the Sequence Listing and distinguish the generic invention as claimed from other nucleic acids, and also describe functional outcomes (a biological activity of the enzyme) that are associated with those structural features. The remaining claims describe the invention in product-by-process terms. Such a manner of claiming a generic invention is entirely proper. See, *Enzo Biochem, Inc. v. Gen-Probe, Inc.*, 63 USPQ2d 1609 (Fed. Cir. 2002). Accordingly, it is inappropriate to apply the instant rejection to the presently-pending claims.

The Examiner has at this time introduced the *Wallach* case in an attempt to shore up his untenable position. The present facts are very far removed from those of *Wallach*, and so *Wallach* has no bearing on the present application.

Wallach relates to a claim to any and all genes encoding a TNF cytotoxic activity, which claims are based on description of only the amino-terminal portion of the TNF protein. No DNA sequences were provided, nor was even any full-length protein sequence provided. The *Wallach* panel decided that, on these facts, adequate description of any and all genes encoding a TNF cytotoxic activity was not provided.

On the other hand, in the present application at least two complete sequences of raffinose synthase genes are provided (i.e. SEQ ID NOS: 1 and 3), as are their translated amino acid sequences (SEQ ID NOS: 2 and 4). Furthermore, the present specification lists several PCR primers that may be used to produce additional raffinose synthase genes from DNA of additional plants and this process and two working examples of it are described (as SEQ ID NOS: 5-8).

Thus, far more information about the nucleic acids of the invention is disclosed in the present application than in the application considered in *Wallach*. Applicants submit that the claims as presently written are well-supported by the description in the specification.

The present application also includes “product-by-process” claims that claim the nucleic acids obtained by the described methods. As asserted above, the *Enzo Biochem* case makes quite clear that an invention describable by a process for making it can properly be claimed in such terms. The Examiner does not address this aspect of the present claims.

As to the question of a “structure-function relationship” that defines the genus of the claims, Applicants have explained in their prior response that the structure of a nucleic acid that is within the genus of the invention is defined by its ability to hybridize to a reference sequence,

e.g. SEQ ID NO: 1 (or 3, 5 or 7) under conditions recognized by the art as being highly stringent, and the function of the nucleic acid that is within the invention is that it encodes a protein having the activity of producing raffinose by combining a D-galactosyl group through an $\alpha(1\rightarrow6)$ bond with a hydroxyl group attached to the carbon atom at position 6 of a D-glucose residue in a sucrose molecule. Other claims recite the structure in terms of a defined amino acid sequence encoded by the claimed nucleic acid, or by a defined nucleotide sequence, such defined sequences encompassing all (SEQ ID NOS: 1-4) or a majority (SEQ ID NOS: 5-8) of a raffinose synthase protein or cDNA. Should the Examiner contest the “function” of the proteins encoded by SEQ ID NOS: 5-8, the Examiner is reminded that the language of the claims is that these proteins comprise the recited sequences, and so additional nucleic acid or amino acid sequences may be appended and that these claims are limited to embodiments having the recited enzymatic function.

The Examiner is reminded of the pronouncement of the Court of Appeals for the Federal Circuit in the recent case of *Capon v. Eshhar v. Dudas* 2005 U.S. App. LEXIS 16865 (Fed. Cir. Aug 12, 2005). The Court noted:

The descriptive text needed to meet [the requirements of § 112, first paragraph] varies with the nature and scope of the invention and with the scientific and technical knowledge already in existence. The law must be applied to each invention that enters the patent process, for each patented advance is novel in relation to the state of the science. Since the law is applied to each invention in view of the state of relevant knowledge, its application will vary with differences in the state of knowledge in the field and differences in the predictability of the science.

In the present instance, the state of the science regarding raffinose synthase genes, and technology for isolating nucleic acids from organisms, is considerably advanced compared to that state at the time the *Lilly* case and the guidelines demanding that the structure-function relationship of a protein be delineated in a specification. In the instant case, the invention is far along from a “wish” or “plan” for how to obtain nucleic acids encoding raffinose synthase from plants. In *Wallach* only an N-terminal portion of a protein had been characterized, and the applicants had provided a nucleic acid sequence of only a portion of the protein. In *Lilly* only one cDNA encoding an insulin protein, from rat, had ever been cloned. The state of the art at the time the applications in *Wallach* and *Lilly* were filed was such that obtaining the 5'-end of cDNA sequences was a challenge to a skilled artisan. PCR technology was non-existent (*Lilly*), or in its infancy.

On the other hand, the instant specification includes two complete coding sequences of raffinose synthase cDNAs from two different plant genera, and two nearly complete coding sequences from yet two more plant genera. The specification also describes how to obtain the terminal portions of cDNA when these are missing and a commercially available kit for doing so (see e.g., page 37, lines 18-22). Thus, regardless of whether the complete cDNA sequence is actually provided in the specification, there can be no doubt that the teachings of the specification place the public in “possession” of the complete sequences of four different raffinose synthase cDNAs from diverse plant genera. It is not necessary for the specification to provide detailed description of particular domains of the raffinose synthase protein that provide for its enzymatic activity

as one of ordinary skill in the art can readily obtain cDNA encoding the entire protein utilizing the teachings of the instant specification. Furthermore, using the set of primers and the other teachings disclosed in the instant specification, the artisan of ordinary skill can readily isolate nucleic acids encoding raffinose synthase proteins from diverse plant genera, as is demonstrated in the working Examples.

Plainly the inventors, and thereby the public, were in possession of the invention as it is presently claimed at the time the instant application was filed.

For all of the above reasons, Applicants submit that the present claims are well-described by the instant specification and the present rejection of claims 48-77 under 35 U.S.C. § 112, first paragraph, for alleged lack of written description support, should be withdrawn.

Claims 46-77 stand rejected for alleged lack of enablement by the disclosure of the specification. This rejection is respectfully traversed. Reconsideration and withdrawal thereof are requested.

Applicants have provided a detailed explanation of how the specification enables the skilled artisan to make and use the presently-claimed invention, applying the factors for consideration set forth in *In re Wands*, in their prior papers filed March 4, 1999 and November 15, 2004. Applicants submit that proper consideration of the *Wands* factors leads one to a finding that no undue experimentation is required to practice the presently claimed invention and that the instant rejection is untenable and should be withdrawn.

However, the Examiner has not yet been persuaded. Once again, the Examiner presents a position is that one of ordinary skill in the art cannot predict if a particular nucleic acid sequence encodes a raffinose synthase protein. In two pages of argument, the Examiner merely expounds his view that he has sufficiently established that the instantly claimed nucleic acids include within their structural scope nucleic acids that encode proteins having other activities, that it is not predictable that any given cloned nucleic acid encodes a protein having raffinose synthase activity and his conclusion that undue experimentation is required for one of ordinary skill in the art to tell the difference between a nucleic acid encoding a raffinose synthase protein and one encoding either stachyose synthase or a seed imbibation protein.

First, the Examiner's initial premise is incorrect. As explained in detail previously, above and in Mr. Nagasawa's Declaration, nucleic acids encoding raffinose synthases are distinguishable at the sequence identity level from nucleic acids encoding STSs or SIPs.

Second, the Examiner admits that one of ordinary skill in the art expects to have to perform screening experiments to confirm that any particular nucleic acid, once isolated or transformed into an organism, actually encodes the intended protein. (See, Page 7, lines 12-20 of the present Office Action.) The Examiner's position, stated as a mere conclusion without any

analysis of the matter, is that despite the detailed guidance provided by the instant specification about how to perform such screening and confirmation¹, it is undue experimentation.

Applicants again remind the Examiner of the holding of the *Wands* case that expected experimentation, the manner of conduct of which is described in a specification, is not undue experimentation and therefore the Examiner's position is incorrect as a matter of law.

Furthermore, the Examiner mischaracterizes the experimentation described in the specification as merely random trial and error. To the contrary, the specification teaches that a particular nucleic acid should be isolated by the methods disclosed, i.e. by amplification of nucleic acids obtained from plants or another organism, preferably using the primers disclosed in the application and nucleic acids from the target organism as a template. Thus, even at this initial step, there is no "random" aspect to the experimentation. Following the teachings of the specification, specific PCR products will be obtained from organisms highly likely to express a raffinose synthase protein.

¹ From Applicants' paper of November 14, 2004:

[T]he specification discloses in detail how to clone DNAs encoding putative raffinose synthase enzymes. The specification provides details such as organisms likely to be useful for isolating template genomic DNA or cDNA (see, e.g. page 1, lines 9-14) and methods for cloning DNA encoding a putative raffinose synthase enzyme from an RNA fraction, including an extensive list of primers that can be utilized for PCR amplification from templates obtained from different organisms (see, e.g. page 10, line 11 to page 18, line 14). The specification describes methods for expressing the cloned DNA in plant cells and in bacteria (see, e.g. page 24, line 3 to page 27, line 23) and an example of expression in bacteria (Example 8 beginning at page 39). The specification describes how to purify raffinose synthase from plant cells (see, e.g. Example 3 beginning on page 32). The specification describes a biochemical assay for raffinose synthase, referring to the Lehle article noted above and summarizing the procedure in Example 2 beginning at page 31.

The specification also provides a number of working examples of isolation of partial or complete raffinose synthase genes from a number of different plants. See, Examples 7 and 9 to 11) and of transformation of a plant (soybean) with a cloned DNA encoding a raffinose synthase (Example 13).

Then, once a nucleic acid has been obtained, it is expressed in some organism. Example 7 of the specification demonstrates expression in *E. coli*. The expressed protein is then assayed for raffinose synthase activity as described in Example 2 of the specification.

Thus, there is nothing at all “random” or “trial and error” about the experimentation described in the instant specification.

For the reasons above, and as explained in Applicants’ previous papers, the rejection of claims 46-77 under 35 U.S.C. § 112, first paragraph, for lack of enablement by the specification, should be withdrawn.

The present application well-describes and claims patentable subject matter. The favorable action of allowance of the pending claims and passage of the application to issue is respectfully requested.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Mark J. Nuell (Reg. No. 36,623) at

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the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

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Respectfully submitted,

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Attachment: Declaration under 37 C.F.R. 1.132 by Mr. Akitsu Nagasawa